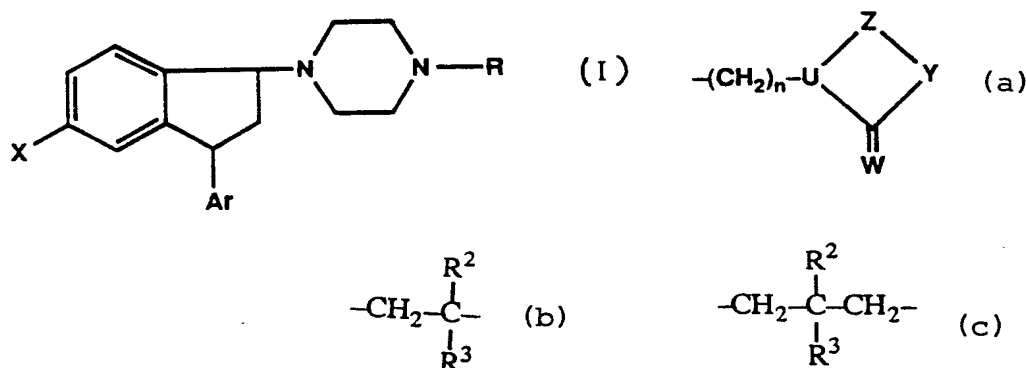




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| (21) International Application Number: PCT/DK91/00358 (22) International Filing Date: 28 November 1991 (28.11.91) (30) Priority data: 2869/90 4 December 1990 (04.12.90) DK (71) Applicant (for all designated States except US): H. LUND-BECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Copenhagen-Valby (DK). (72) Inventors; and (75) Inventors/Applicants (for US only) : BØGESØ, Klaus, P. [DK/DK]; Mølleåparken 15, DK-2800 Lyngby (DK). BREGNEDAL, Peter [DK/DK]; Gærdesmuttevej 1B, DK-3450 Allerød (DK). | (74) Agent: PETERSEN, John, Meidahl; Patent Department, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Copenhagen-Valby (DK). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU ⁺ , US. Published <i>With international search report.</i> | |

(54) Title: INDAN DERIVATIVES**(57) Abstract**

5-Substituted trans-1-piperazinoindan derivatives having general formula (I), wherein X is halogen, trifluoromethyl, alkyl, alkylthio, alkyloxy, hydroxy, alkylsulphonyl, alkyl- or dialkylamino, trifluoromethylthio or cyano; R is hydrogen, or alkyl, alkenyl, cycloalkyl, or cycloalkyl lower alkyl, optionally substituted with hydroxy, or R is a substituent (a), wherein n is an integer from 1 to 6; U is CH or N; Y is CH₂, O, S or N-R¹, R¹ being hydrogen or cycloalkyl, cycloalkylmethyl, alkyl or alkenyl optionally substituted with hydroxy or an optionally substituted phenyl group; W is O or S; Z is $-(CH_2)_4-$, (b), (c), where R² and R³ are hydrogen or lower alkyl, $-CH=CH-$, $-CH=CH-CH_2-$, optionally substituted 1,2-phenylene, 1,2-C₆H₄CH₂- (to form a quinazolidinone or -thione ring system) or 1,2-C₆H₄CO- (to form a quinazolidindion or thioxoquinazolidinon ring system); and Ar is an optionally substituted phenyl, thiophene or furane ring; are selective, centrally acting 5-HT₂ antagonists useful in the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia and migraine.

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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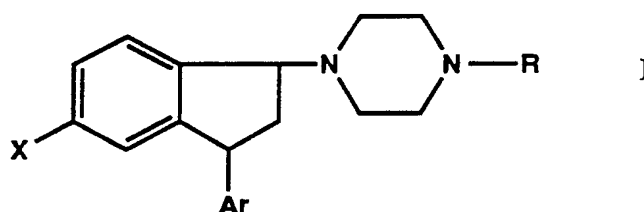
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INDAN DERIVATIVES

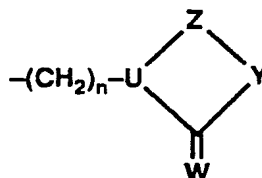
The present invention relates to 5-substituted 1-piperazinoindan derivatives and acid addition salts thereof with selective antagonistic action on the serotonin-2 (5-hydroxytryptamin-2; 5-HT₂) receptors in the central nervous system, to medicaments comprising such derivatives as active ingredients, to the use of such derivatives in the treatment of diseases in the central nervous system and to methods for the preparation of such compounds.

- 10 The novel piperazinyindan derivatives of the invention are trans-isomers represented by the following Formula I :



wherein X is halogen, trifluoromethyl, lower alkyl, lower alkylthio, lower alkoxy, hydroxy, lower alkylsulphonyl, lower alkyl- or dialkylamino, trifluoromethylthio or a
15 cyano group;

R is hydrogen, lower alkyl or alkenyl, cycloalkyl, or cycloalkyl lower alkyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour
20 carbon atoms inclusive, or R is a substituent



wherein n is an integer from 1 to 6;

U is CH or N;

Y is CH₂, O, S or N-R¹, R¹ being hydrogen or a cycloalkyl or a cycloalkylmethyl or a
25 lower alkyl or alkenyl group optionally substituted with one or two hydroxy groups or a phenyl group optionally substituted with halogen, trifluoromethyl or lower alkyl;

W is O or S;

Z is $-(CH_2)_4-$, $-\text{CH}_2-\overset{\overset{R^2}{|}}{\underset{\underset{R^3}{|}}{C}}-$, $-\text{CH}_2-\overset{\overset{R^2}{|}}{\underset{\underset{R^3}{|}}{C}}-\text{CH}_2-$, wherein R^2 and R^3 are hydrogen or lower

alkyl, $-\text{CH}=\text{CH}-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, 1,2-phenylene, optionally substituted with halogen
5 or trifluoromethyl, or if U is nitrogen and Y is NR^1 Z may also be 1,2- $\text{C}_6\text{H}_4\text{CH}_2-$ (to form a quinazolidinone or -thione ring system) or 1,2- $\text{C}_6\text{H}_4\text{CO}-$ (to form a quinazolidindion or thioxoquinazolidinon ring system); and

Ar is a phenyl ring optionally substituted with halogen, trifluoromethyl or lower alkyl
10 or Ar is a thiophene or furane ring optionally substituted with lower alkyl.

The term "lower alkyl" is intended to mean a straight or branched alkyl group having from one to four carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, etc. Lower alkoxy, lower alkylthio, lower alkylsulfonyl, lower alkylamino
15 and lower dialkylamino similarly designate such groups wherein the alkyl moiety is a lower alkyl group as defined above.

Lower alkenyl is intended to mean an alkenyl group containing from 2 to 4 carbon atoms, for example ethenyl, 1-propenyl, 2-butenyl, etc.

20

Cycloalkyl is intended to mean cycloalkyl having from 3 to 8 carbon atoms incl. in the ring.

The Z-group may be oriented in both directions in the ring.

25

Halogen means fluoro, chloro, bromo or iodo.

When Y is NR^1 wherein R^1 is H, the compound may exist in tautomeric form, i.e. wherein W is $-\text{OH}$ or $-\text{SH}$, respectively, connected to the ring via a single bond, and
30 having a double bond in the ring, i.e. from the Y to the carbon atom bearing the $-\text{OH}$ or $-\text{OS}$ group. Such tautomeric forms are intended to be embraced by Formula I.

Compounds similar to the compounds of the present invention are disclosed in our own US patent No. 4,443,448 which relates to 1-piperazino-3-phenylindan derivatives having one substituent in the benzen moiety of the indan ring system and claimed to have neuroleptic or antidepressant activity. The neuroleptic activity of the compounds is based on tests showing dopamine antagonistic activity *in vivo* whereas antidepressant activity is shown by the ability of the compounds to inhibit the reuptake of dopamine. A number of the compounds of the general Formula I of the present invention are generically embraced by the general scope of said patent. However, only a few of the 5-substituted derivatives of the general Formula I of the present invention are specifically mentioned in said patent. All of said compounds are compounds of the general Formula I wherein Ar is 4-fluorophenyl R is lower alkyl optionally substituted with hydroxy. Only some of said compounds were tested and they were all found to be without significant activity as dopamine antagonists in the *in vivo* test used, cf. Table 8 of said patent. Accordingly they were regarded to be without value as neuroleptics. No results as to dopamine reuptake inhibiting effects are given for those compounds.

Our own US patent No. 4,684,650 discloses a series of optionally 6-substituted 1-piperazino-3-phenylindans claimed to have a potent antiserotonergic activity without having any significant neuroleptic activity. It was shown that the compounds had a high affinity to 5-HT₂ receptors whereas they were weak or inactive in an *in vivo* model for antidopaminergic effect, i.e. the methylphenidate antagonism test. Many of the compounds were shown to have potent antihypertensive action. In a later publication about the same series of compounds (K.P. Bøgesø et al., J.Med.Chem., 1988, 31, 2247) it was shown that in despite of a selective antiserotonergic profile *in vivo*, nevertheless many of the compounds still had significant activity for both dopamine D-2 receptors and in particular α_1 adrenoceptors.

The 5-HT₂ antagonist ritanserin (Meert, T. F.; Janssen, P. A. J. *Drug. Dev. Res.* 1989, 18, 119.) has been shown to be effective in the treatment of anxiety and depression presumably through improvement of the sleep quality. Furthermore, selective, centrally acting 5-HT₂ antagonists have been shown to have an effect towards the negative symptoms of schizophrenia and to reduce extrapyramidal side-effects caused by treatment with classical neuroleptics in schizophrenic patients

(Gelders, Y.G., British J. Psychiatry, 1989, 155 (suppl.5), 33). Finally, selective 5-HT₂ antagonists could be effective in the prophylaxis of migraine since it is known that 5-HT is involved in migraine attacks. The links between 5-HT and migraine attacks are several and they suggest a number of mechanisms whereby 5-HT may be involved (Scrip Report; "Migraine – Current trends in research and treatment"; PJB Publications Ltd.; May 1991). Various 5-HT₂ antagonists are in clinical trials as anti-migraine agents, such as sergolexole (c.f. for example Pharma Projects, May 1991, 1359-1365). Obviously there is a strong demand for selective 5-HT₂ antagonists without side effects.

10

It has now surprisingly been found that the 5-substituted 1-piperazinoindan derivatives of Formula I, have high affinity for 5-HT₂ receptors. As compared to the corresponding 6-substituted derivatives they have very low affinity to both dopamine D-2 receptors and α_1 adrenoceptors. *In vivo* the compounds have potent activity in animal models for central 5-HT₂ antagonism. Because of the very low affinity for α_1 adrenoceptors the 5-substituted compounds have, in contrast to the 6-substituted derivatives, substantially no effect on the blood pressure.

Only trans-isomers of the 5-substituted 1-piperazinoindan derivatives of Formula I are active, cis-isomers being without significant 5-HT₂ antagonistic activity.

Accordingly in a first aspect the present invention relates to trans-isomers of the compounds having the general Formula I as defined above and pharmaceutically acceptable acid addition salts thereof and prodrugs therefore with the proviso that R may not be hydrogen or lower alkyl or alkenyl optionally substituted with hydroxy when Ar is optionally substituted phenyl.

The trans-isomers of the invention exist as pairs of optically active isomers and such isomers are within the scope of the present invention. Also any other stereoisomer of a compound having the general Formula I is embraced by the invention. It has so far been found that the 5-HT₂ antagonistic activity predominantly resides in one of the optical isomers.

Prodrugs of the present invention may be conventional esters when hydroxy groups are available, or in particular if the compound is a compound of the general Formula I wherein W is O and Y is NR¹, R¹ being hydrogen, the prodrug may be a reaction product with an acid or an activated acid, with formaldehyde alone or in the presence of an alcohol or an amine, or with an acyloxymethylene halide, which product accordingly may be represented by a formula similar to the general Formula I defined above wherein W is O, Y however being a group NR^{1'} wherein R^{1'} designates a group -A-B where A is selected from CO, CS, or CH₂, and if A is CO or CS, B is selected from the groups consisting of:

- 10 i) hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl or cycloalk(en)ylalk(en)yl, optionally substituted with one or two hydroxy groups, or phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, acyloxy, or cyano; or
 - 15 ii) QB¹, wherein Q is O or S and B¹ is selected from the substituents defined for B under i) above except hydrogen; and
 - iii) NB²B³, wherein B² and B³ independently are selected from the substituents defined for B¹ under ii) above, or B² and B³ are combined to form a four to eight membered heterocyclic ring containing from one to three nitrogen atoms and
 - 20 from zero to three oxygen or sulfur atoms; or
- if A is CH₂, B is selected from the groups consisting of:
- iv) a group QB¹ as defined in ii);
 - v) a group NB²B³ as defined in iii); or
 - vi) a group OC(O)B⁴, wherein B⁴ is as defined for B¹.

25

Although the latter prodrugs are not esters, they would decompose properly in order to release the compound of the invention over a desired period of time when administered parenterally as a depote formulation in an appropriate oil, such as coconut oil, e.g. viscoleo®, peanut oil, sesame oil, cotton seed oil, corn oil, soy bean

30 oil, olive oil, etc. or synthetic esters of fatty acids and glycerol or propylenglycol.

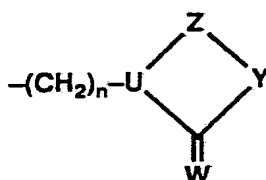
The pharmaceutically acceptable acid addition salts of the compounds used in the invention are salts formed with non-toxic organic or inorganic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic,

succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The compounds of the invention show high affinity to 5-HT₂ receptors and very low receptor affinity to D-2 receptors and α₁ adrenoceptors and consequently they are very selective with respect to the 5-HT₂ receptor. Accordingly, they are useful in the treatment of various diseases of the central nervous system, such as anxiety, depression, sleeping disorders, negative symptoms of schizophrenia, extrapyramidal side-effects caused by treatment with classical neuroleptics, and migraine.

Preferred 5-substituted trans-1-piperazinoindan derivatives according to the invention are those wherein:

Ar is a phenyl ring optionally substituted with halogen or methyl, preferably 4-fluorophenyl; X is Cl or F and/or R is a group of the formula:



wherein n is 2,

U is nitrogen; W is O or S; Z is -CH₂-CH₂- or -CH₂-CH₂-CH₂-; and

Y is a group NR¹ wherein R¹ is hydrogen or lower alkyl.

Most preferably the compound of the invention is selected from the group of:

- (-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone, dimaleate;
- (+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinethione, dihydrochloride;
- (-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1H)-pyrimidinethione, dihydrochloride;

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; and
(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate.

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In a second aspect the present invention relates to a pharmaceutical preparation comprising at least one derivative of the general Formula I as defined above together with a pharmaceutically acceptable carrier or diluent.

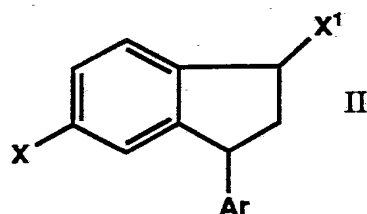
- 10 The compounds of the Formula I and the pharmaceutically acceptable acid addition salts thereof may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection.
- 15 Suitable pharmaceutical preparations may be prepared by methods well known in the art. Conveniently, the compounds of the invention are administered in unit dosage form containing said compound in an amount of about 0.05 - 100 mg, preferably about 1 - 50 mg.
- 20 The total daily dose usually ranges from about 0.1 to 500 mg of the active compound of the invention.

In a further aspect the present invention relates to the use of a compound having the general Formula I as defined above for the manufacture of a medicament for
25 the treatment of a disease in the central nervous system, preferably anxiety, depression, sleeping disorders, negative symptoms of schizophrenia, extrapyramidal side-effects caused by treatment with classical neuroleptics, and migraine.

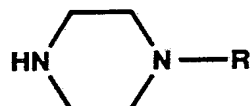
The invention moreover relates to a method for the preparation of the novel
30 5-substituted derivatives of Formula I, which comprises:

a) treating a compound of the following Formula II:

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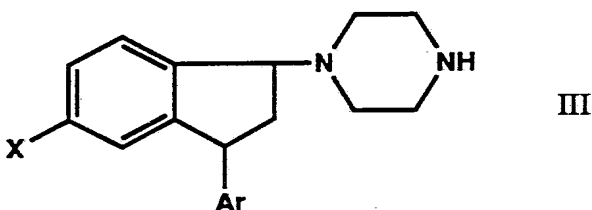


with a piperazine derivative of formula:



- 5 in which formulas X, Ar and R are as defined above, and X¹ is halogen or -OSO₂R⁴ wherein R⁴ is alkyl such as CH₃ or aryl such as p-toluy!

b) treating a compound of the following Formula III:

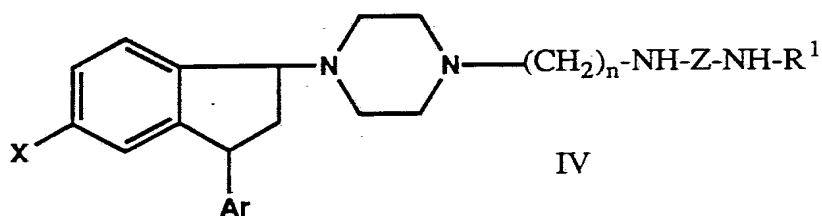


- 10 wherein X and Ar are as defined above, with a compound of the formula X¹-R wherein R and X¹ are as defined above except that R cannot be hydrogen;

c) treating a compound of Formula III with a compound R'-CHO, wherein R' is such a group that R'-CH₂- is as defined above for R, in the presence of a reducing agent;

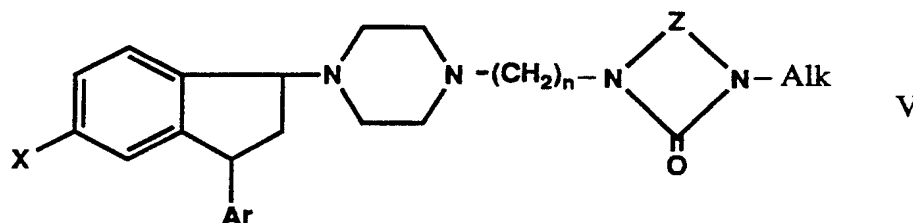
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d) treating a compound of the following Formula IV:



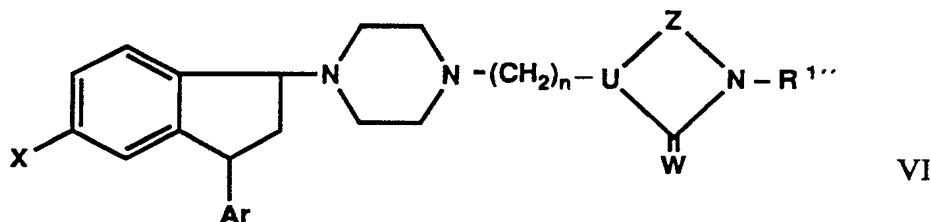
wherein X, Ar, R¹, Z and n are as defined above, with CS₂, thiophosgene, urea or
20 phosgene;

e) treating a compound of the following Formula V:



wherein X, Ar, n, and Z are as defined above and Alk is an alkali metal such as sodium or potassium, with a compound of formula R⁵-X¹ wherein R⁵ is a lower alkyl group and X¹ is as defined above;

f) reducing a compound with the following Formula VI:



wherein X, Ar, n, U, Z and W are as defined above and R' is a cycloalkyl or lower alkyl group containing one or more ester, ketone or aldehyde groups, with a suitable reducing agent to a corresponding compound wherein R¹ is a lower alkyl or a cycloalkyl group containing one or more hydroxy groups;

g) reacting a compound of Formula I wherein R is a group of the formula:



wherein n, U, Z and Y are as defined above and W is O, with P₂S₅ or Lawessons reagent to obtain the corresponding compound wherein W is S.

Method a) is preferably carried out in an inert solvent such as acetone or methyl-
20 isobutylketone using either an excess of the piperazine reactant or by using equimolar amounts of reactants in the presence of an alkali metal carbonate such

as potassium carbonate or another alkaline substance at reflux temperatures.

Method b) is preferably carried out in an inert solvent such as ethanol or isobutylketone in the presence of an alkali metal carbonate such as potassium carbonate or
5 another alkaline substance at reflux temperatures.

Method c) is preferably carried out in an inert solvent such as an alcohol (eg methanol) or an ether (eg tetrahydrofuran) by hydrogenation in the presence of a suitable catalyst such as Pt or Pd or by using a borohydride such as NaCNBH_3 at a
10 pH of 5-6.

Method d) is preferably carried out by treating a compound of Formula IV in an inert solvent, such as n-pentanol or n-butanol, with urea or carbon disulfide succeeded by heating at reflux temperatures.

15

In Method e), the alkalimetal salt of Formula V is preferably formed by treating the corresponding hydrogen derivative with an alkali metal alkoxide such as potassium tert.-butoxide in an inert solvent such as toluene whereupon the salt is reacted directly with the alkylating agent, $\text{R}^5\text{-X}^1$, at room or higher temperatures.

20

Method f) is preferably carried out by reducing the derivative of Formula VI with a suitable reducing agent such as lithium or sodium borohydride in an inert solvent such as tetrahydrofurane.

25 Method g) is preferably carried out in hexamethyl phosphorous triamide (HMPA) or xylene at temperatures between 110 °C and 200 °C.

The acid addition salts of the compounds of the invention are easily prepared by methods well known in the art. The base is reacted with either the calculated
30 amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or with an excess of the acid in an aqueous immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts.

The preparation of the compounds of Formula II from the corresponding 2,3-dihydro-inden-1-ones may be carried out analogously with the method described in U.S. Patent No. 4,443,448, U.S. Patent No. 4,684,650, and J. Med. Chem. **1983**, 26, 935. The indanones were either prepared by cyclization of the corresponding
5 diphenylpropionic acids or more conveniently as described for similar compounds in U.S. Patent No. 4,873,344 and in J. Org. Chem. **1990**, 55, 4822 from the proper 3,5-disubstituted 1-amino-3-cyano-1-inden-2-carboxylic acid esters which in turn also may be prepared as described in U.S. Patent No. 4,873,344. Hereby the following novel 3,5-disubstituted 1-amino-3-cyano-1-inden-2-carboxylic acid esters were
10 prepared:

1-Amino-3-cyano-3-(4-fluorophenyl)-5-methyl-1-inden-2-carboxylic acid methyl ester, mp 215-217 °C.

15 1-Amino-5-chloro-3-cyano-3-phenyl-1-inden-2-carboxylic acid methyl ester, mp 192-194 °C.

1-Amino-5-chloro-3-cyano-3-(2-fluorophenyl)-1-inden-2-carboxylic acid methyl ester, mp 227-228 °C.

20

1-Amino-5-chloro-3-cyano-3-(3-fluorophenyl)-1-inden-2-carboxylic acid methyl ester, mp 191-193 °C.

1-Amino-5-chloro-3-cyano-3-(2-methyl-4-thienyl)-1-inden-2-carboxylic acid methyl
25 ester, mp 161-163 °C.

1-Amino-5-chloro-3-cyano-3-(4-chlorophenyl)-1-inden-2-carboxylic acid methyl ester, mp 213-215 °C.

30 1-Amino-5-chloro-3-cyano-3-(4-methylphenyl)-1-inden-2-carboxylic acid methyl ester, mp 228-230 °C.

By the above method the following novel 2,3-dihydro-1*H*-inden-1-ones were prepared:

3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one, mp 105-106 °C

3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-one, mp 69-71 °C.

5 5-chloro-3-phenyl-2,3-dihydro-1*H*-inden-1-one, mp 127-129 °C.

5-chloro-3-(2-fluorophenyl)-2,3-dihydro-1*H*-inden-1-one, mp 83-85 °C.

5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1*H*-inden-1-one, mp 118-120 °C.

10

3-(4-fluorophenyl)-5-methylthio-2,3-dihydro-1*H*-inden-1-one, mp 74-76 °C.

5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-one, mp 101-102 °C.

15 5-chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-one, mp 140-142 °C.

5-chloro-3-(4-methylphenyl)-2,3-dihydro-1*H*-inden-1-one, mp 112-114 °C.

As previously described (see references cited above) the 2,3-dihydro-1*H*-inden-1-ones may be reduced with sodiumborohydride to the corresponding cis-2,3-dihydro-1*H*-inden-1-ols which serves as the starting materials for preparing the compounds of Formula II. The following new 2,3-dihydro-1*H*-inden-1-ols were obtained:

3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-ol, mp 81-83 °C.

25

3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-ol, mp 100-102 °C.

5-chloro-3-phenyl-2,3-dihydro-1*H*-inden-1-ol, mp 110-111 °C.

30 5-chloro-3-(2-fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 78-80 °C.

5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 110-112 °C.

3-(4-fluorophenyl)-5-methylthio-2,3-dihydro-1*H*-inden-1-ol, mp 114-116 °C.

5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-ol, mp 119-121 °C.

5-chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 129-131 °C.

5

5-chloro-3-(4-methylphenyl)-2,3-dihydro-1*H*-inden-1-ol, mp 107-109 °C.

In the following, the invention is further illustrated by way of examples which must in no way be construed as limiting for the invention.

10

EXAMPLES

EXAMPLE 1

15

Trans -1-[2-[4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazinyl]ethyl]-2-imidazolidinone. dimaleate (Compd. 1)

A mixture of 1-Chloro-3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden
20 (8.5 g) and 1-[(2-(piperazin-1-yl)ethyl]-2-imidazolidinone (20 g) in methylisobutyl-
ketone (250 ml) was stirred at 80°C for 18 hours.

The reaction mixture was cooled, whereupon ether and water was added. The
phases were separated, and the organic phase was washed with water. The ether
25 phase was extracted with 1 N methane sulphonic acid. The base was liberated with
10 N sodium hydroxide and extracted with methylene chloride. The organic phase
was dried (MgSO₄) and evaporated in vacuo to give 10 g of crude 1. The crude
base was dissolved in acetone and transformed to the maleate salt which was
recrystallized from ethanol (100 ml) to give 4.9 g of 1, as dimaleate ; mp 169-171°C.

30 CHN calculated: 55.92%; 5.13%; 7.91%.

CHN found: 55.94%; 5.02%; 7.94%.

EXAMPLE 2

Preparation of (+)-1 (the active enantiomer of 1)

- 5 To a solution of trans-1-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine (38 g) in ethanol (500 ml) was added a solution of L-(+)-tartaric acid (15 g) in water (25 ml). The mixture was left overnight at room temperature. The crystals were filtered and recrystallized from methanol (400 ml) and water (400 ml) to give 17 g; mp 221-223°C. Optical rotation of the base: $[\alpha]_D = -3.2^\circ$ (c 0.5, MeOH).

10

- The first filtrate from the L-(+)-tartrate salts was evaporated in vacuo and converted to the base. This base (25 g) was dissolved in methanol (400 ml) and a solution of D-(-)-tartaric acid (10 g) in water (50 ml) was added. The mixture was kept for 2 hours at room temperature. The crystals were filtered and recrystallized from methanol
15 (250 ml) and water (250 ml) to give 13 g, mp 222-224°C. Optical rotation of the base: $[\alpha]_D = +3.7^\circ$ (c 0.5, MeOH).

- The D-(-)-tartrate salt was converted to the base (9.5 g) which was added to a mixture of 1-(2-chloroethyl)-2-imidazolidinone (9 g), potassium carbonate (10 g) and
20 potassium iodide (0.5 g) in methylisobutylketone (250 ml). The mixture was refluxed with stirring for 18 hours. The reaction mixture was worked up as described in Example 1, to give a crude base (15 g). The base was converted to the dimaleate salt which was recrystallized three times from ethanol to give (+)-1, dimaleate salt, mp 158-159°C. $[\alpha] = +5.5^\circ$ (c 0.5, CH₃OH).
- 25 CHN calculated: 55.92%; 5.13%; 7.91%.
CHN found: 55.92%; 5.09%; 7.95%.

EXAMPLE 3

- 30 Optical resolution of Trans-4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazine ethanol (Compd.2)

The dihydrochloride salt of Compd.2 (11 g, c.f. U.S. Patent 4,443,448) was conver-

ted to the base (9.5 g). A solution of the base and L-(+)-tartaric acid (4 g) in ethanol (250 ml) was kept at room temperature for 18 hours. The crystals were filtered off and dried (4.5 g), and recrystallized from methanol (600 ml) to give 3.2 g ; mp 216-217°C ; $[\alpha]_D = +15.4^\circ$ (c 0.5, DMSO). The L-(+)-tartrate salt was converted to the
5 base, which was transferred to the dihydrochloride salt. The dihydrochloride salt was recrystallized from ethanol/ether to give 1 g of (+)-2, dihydrochloride; mp 224-226°C; $[\alpha]_D = +27.1^\circ$ (c 0.5, CH₃OH).

The first filtrate from the L-(+)-tartrate salt was evaporated and converted to the base. The base was converted to the D-(-)-tartaric salt which was recrystallized and
10 converted to the dihydrochloride salt as described for (+)-2.

0.6 g of (-)-2, dihydrochloride was obtained ; mp 223-226°C ; $[\alpha]_D = -27.1^\circ$ (c 0.5, CH₃OH).

Trans-4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazine-
15 ethanol (3 , c.f. US Patent 4,443,448) was resolved in a similar way to give

(+)-3, dihydrochloride ; mp 224-227°C ; $[\alpha]_D = +13.5^\circ$ (c 0.5, H₂O) and

(-)-3, dihydrochloride ; mp 224-227°C ; $[\alpha]_D = -14.1^\circ$ (c 0.5, H₂O).

20 The method described in Example was used for the preparation of the following compounds:

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine-1-yl]ethyl]-2-imidazolidinone; mp 168-170 °C. Compd. 4.

25

Trans-4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazineethanol, dimaleate; mp 172-174 °C. Compd. 5.

Trans-4-[5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-yl]-1-piperazineethanol, dimaleate; mp 175-177°C. Compd. 6.
30

Trans-1-[2-[4-[5-chloro-3-(2-methyl-4-thienyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine-1-yl]ethyl]-2-imidazolidinone, dimaleate; mp 174-176 °C. Compd. 7.

Trans-4-[3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-yl]-1-piperazine
ethanol, dimaleate; mp 169-171 °C. Compd. 8.

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-yl]piperazine-1-
5 yl]ethyl]-2-imidazolidinone, dimaleate; mp 180-181 °C. Compd. 9.

EXAMPLE 4

Trans-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazine, maleate
10 (Compd. 10)

Thionylchloride (44 ml) was added dropwise with water-cooling to a solution of 5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol in ether (2L) with a catalytic amount of DMF (0.5 ml). Then the mixture was stirred for 2 hours at room temperature, poured into ice and neutralized with 9N NaOH. The organic phase was
15 separated, dried (MgSO₄) and evaporated to give 140 g of crude 1,5-dichloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden.

A mixture of the chloroderivative (140 g), piperazine (800 g) and acetone (2L) was
20 refluxed with stirring for 18 hours. After cooling piperazine hydrochloride was filtered off and washed with ethyl acetate. The combined filtrate was concentrated in vacuo. The residue was dissolved in ether, washed with water and extracted with 1N methane sulphonic acid. The base was liberated from the acid extract with 9N sodium hydroxide, extracted with ether, dried (MgSO₄) and evaporated in vacuo to
25 give crude Compd.10 (156 g). The residue was dissolved in acetone (600 ml) and ethanol (600 ml), whereupon maleic acid (110 g) was added. After 1 hour at room temperature the maleate salt of Compd.10 was filtered and dried. Yield: 216 g ; mp 190-191°C.

10 g were recrystallized from ethanol to give pure Compd. 10, maleate; mp: 194-
30 195°C.

CHN calculated: 61.81%; 5.42%; 6.27%.

CHN found: 61.77%; 5.40%; 6.34%.

EXAMPLE 5Optical resolution of Compd.10 ((+)-10 and (-)-10)

- 5 A solution of Compd.10 (24 g) and (-)-dibenzoyl-L-tartaric acid hydrate ((-)-DBT) (27.3 g) in acetone (250ml) was left for 18 hours at room temperature. The crystals were filtered and dried. The (-)-DBT salt was boiled with methanol (1L), cooled, filtered and dried to give 13.5 g of (-)-DBT salt; mp: 213-214°C.
- The first filtrate from the (-)-DBT salt was concentrated and converted to the base 10 (13 g), which was treated with (+)-DBT in the same manner as described for the (-)-DBT salt. Yield: 11 g of (+)-DBT salt; mp: 212-213°C.
- The DBT salts were converted to the bases and then precipitated as maleate salts. The maleate salts were recrystallized from ethanol (200 ml) and methanol (50 ml) to give
- 15 (+)-10 , maleate salt ; mp: 194-196°C ; $[\alpha]_D = +30.6^\circ$ (c 0.5, CH₃OH).
- (-)-10 , maleate salt ; mp: 194-196°C ; $[\alpha]_D = -30.2^\circ$ (c 0.5, CH₃OH).

EXAMPLE 6

20

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]-ethyl]-3-isopropyl-2-imidazolidinone, dimaleate (Compd.11)

A mixture of Compd.10 (140 g as the maleate salt , see Example 4), 1-(2-
25 chloroethyl)-3-isopropyl-2-imidazolidinone (75 g), potassium carbonate (260 g) and potassium iodide (5 g) in methylisobutylketone (1L) was refluxed with stirring for 18 hours.

After cooling, water (500 ml) was added. The phases were separated and the
30 organic layer was washed with water and then concentrated in vacuo. The residue was dissolved in ether, washed with water and extracted with 1N methane sulphonic acid. The base was liberated with 9N NaOH, extracted with ether, dried and concentrated in vacuo to give 157 g of crude Compd.11. The base was converted to the dimaleate salt in ethanol (2L) to give 193 g of trans-isomer (11).

A sample recrystallized from methanol melted at 188-190°C.

CHN calculated: 58.61%; 5.92%; 7.81%.

CHN found: 58.78%; 5.90%; 7.88%.

5 EXAMPLE 7

Optical resolution of Compd.11 ((+)-11 and (-)-11)

The resolution was performed essentially as described in the Examples 2 and 3
10 (using L-(+)- and D-(-)-tartaric acid) with the exception that tartrate salts were crystallized and recrystallized from water. From 126 g of 11 (as the base) there was obtained 50 g of D-(-)-tartrate, mp 102-104°C, and 51 g of L-(+)-tartrate, mp 102-104°C.

In a conventional manner the tartrate salts were converted to the maleate salts
15 which were recrystallized from ethanol to give

(+)-11, dimaleate, mp 175°C, $[\alpha]_D = +17.0^\circ$ (c 0.5, CH₃OH), and

(-)-11, dimaleate, mp 175°C, $[\alpha]_D = -17.5^\circ$ (c 0.5, CH₃OH).

The method described in Example 6 was used for the preparation of the following
20 compounds:

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone, dimaleate; mp 178-180 °C. Compd. 12.

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone, dimaleate; mp 174-176 °C. Compd. 13.
25

Trans-3-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-oxazolidinone, diHCl; mp 244-246 °C. Compd. 14.

30 Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-pyrrolidinone, diHCl; mp 250-252 °C. Compd. 15.

Trans-1-[3-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-yl]propan-1-yl]-2-imidazolidinone, dimaleate; mp 159-160 °C. Compd. 16.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-phenyl-2-imidazolidinone,dimaleate; mp 174-176 °C. Compd.17.

- 5 Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-methyl-2-imidazolidinone,dimaleate; mp 164-166 °C. Compd.18.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-ethyl-2-imidazolidinone,dimaleate; mp 178-180 °C. Compd.19.

10

Trans-1-[2-[4-[5-chloro-3-phenyl-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 189-190 °C. Compd.20.

- Trans-1-[2-[4-[5-chloro-3-(2-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 190-192°C. Compd.21.
- 15

Trans-1-[2-[4-[3-(4-fluorophenyl)-5-(methylthio)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-imidazolidinone,dimaleate; mp 182-184 °C. Compd. 22.

- 20 Trans-1-[2-[4-[3-(4-fluorophenyl)-5-(methylthio)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 186-188 °C. Compd. 23.

Trans-1-[2-[4-[5-bromo-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 180-182 °C. Compd. 24.

25

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-benzimidazolin-2-one,dimaleate; mp 192-194 °C. Compd. 25.

- Trans-1-[2-[4-[5-chloro-3-(4-methylphenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 184-186 °C. Compd. 26 .
- 30

Trans-1-[2-[4-[5-chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 170-172 °C. Compd. 27 .

Trans-1-[2-[4-[5-chloro-3-(3-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-3-isopropyl-2-imidazolidinone,dimaleate; mp 180-182 °C. Compd. 28

EXAMPLE 8

5

Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-imidazolidinthione, dimaleate (Compd. 29)

A mixture of Compound 2 (140 g, base, c.f. US Patent 4,443,448), thionyl chloride
10 (100 ml) and DMF (10 ml) in chloroform (2L) was refluxed for 2 hours. After cooling, the hydrochloride salt of the chloroethyl derivative of 2 was filtered, washed with ethyl acetate and dried (Yield: 84 g).

A mixture of 42 g of the hydrochloride salt and ethylenediamine (100 ml) in ethanol
15 (500 ml) was refluxed with stirring for 3 hours. The mixture was concentrated in vacuo; the residue was dissolved in a mixture of methylene chloride and water, the organic layer was separated, washed with saturated NaCl solution, dried (MgSO₄) and evaporated in vacuo to give 40 g of crude trans-1-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-4-[2-[(2-aminoethyl)amino]ethyl] piperazine as an oil.
20 Said ethylenediamine derivative was dissolved in methylene chloride, whereupon carbon disulfide (15 ml) was added. The mixture was kept for 1 hour at room temperature, and was then evaporated in vacuo. The crude dithiocarbamate salt was dissolved in n-pentanol and refluxed for 1 hour (evolution of hydrogen sulfide). The reaction mixture was concentrated in vacuo. The residue was dissolved in
25 ether, extracted with 1N methanesulfonic acid, whereupon the base was liberated with 9N NaOH and extracted with ether. The ether solution was filtered through silica gel, and concentrated to yield 24 g of an oil, which was transformed to the dimaleate to give 29, dimaleate, mp 172-174°C.

CHN calculated: 57.04%; 5.25%; 8.32%.

30 CHN found: 57.30%; 5.43%; 8.17%.

Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dimaleate. mp 174-176 °C., Compd. 30 was prepared in a similar way, by replacing ethylenediamine with 1,3-

propylendiamine. The enantiomers of this compound were prepared in a similar way starting from (+)-2 and (-)-2, respectively:

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 205-206 °C, $[\alpha]_D = +26.7^\circ$ (c 0.5, water). Compd. (+)-30.

(-)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 205-206 °C, $[\alpha]_D = -25.6^\circ$ (c 0.5, water). Compd. (-)-30.

The following compounds was prepared in a corresponding manner:

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-2-imidazolidinthione,dimaleate; mp 183-184 °C. Compd.31.

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dimaleate; mp 184-185 °C. Compd.32 .

(+)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 212-213 °C, $[\alpha]_D = +6.6^\circ$ (c 0.5, water). Compd. (+)-32.

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione,dihydrochloride; mp 212-213 °C, $[\alpha]_D = -6.6^\circ$ (c 0.5, water). Compd. (-)-32.

The following compounds were also prepared as described in Example 8, except that the diamines were treated with urea instead of carbondisulfide. A mixture of the diamine and urea in NMP was heated for 4 h at 140-160 °C, whereupon the reaction mixture was worked-up in a conventional manner.

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-

yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 170-171 °C,
[α]_D = + 16.0° (c 0.5, water). Compd. (+)-33 .

(-)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-
5 yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 170-171 °C,
[α]_D = - 15.0° (c 0.5, water). Compd. (-)-33 .

(+)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-
yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 179-180 °C,
10 [α]_D = + 16.8° (c 0.5, water). Compd. (+)-34.

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-
yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 179-180 °C,
[α]_D = - 17.2° (c 0.5, water). Compd. (-)-34.

15

(±)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin- 1-
yl]ethyl]-5,5-dimethyl-tetrahydro-2(1*H*)-pyrimidinone,dimaleate; mp 166-168 °C,
Compd. 35.

20

EXAMPLE 9

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1-*H*-inden-1-yl]piperazin-1-
yl]ethyl]-3-isopropyl-2-imidazolidinthione, dimaleate (Compd.36)

25

A mixture of 10 (15 g as the base), chloroacetonitrile (4.6 g) and potassium carbonate (10 g) in methyl ethylketone (400 ml) was refluxed overnight with stirring. After cooling and evaporation in vacuo the residue was treated with water and ether. The ether phase was dried and evaporated to give an oil which was chromato-
30 graphed using 100 g of silica gel and ethyl acetate - methanol - triethylamine (80:10:10) as the mobile phase. Yield: 15 g, which was used without further purification.

The acetonitrile derivative (15 g) in dry tetrahydrofurane (150 ml) was treated under cooling with 3 g of pelleted lithium aluminium hydride. The reaction mixture was refluxed for 4 hours and worked-up in a conventional manner to give 15 g of the crude N-(2-aminoethyl) derivative of **10**.

5

Chloroacetylchloride (4.5 g) was added at 10-15°C to a stirred mixture of the aminoethyl derivative (15 g) and triethylamine (15 g) in trichloroethane. The mixture was stirred for 1 hour, whereupon isopropylamine (25 ml) was added. The reaction mixture was refluxed for 5 hours and was then treated with water. The organic

10 phase was evaporated, and the resulting oil was dissolved in dry tetrahydrofurane (250 ml) and was then treated with 4 g of pelleted lithium aluminium hydride. After 2 hours' reflux the reaction mixture was worked-up in a conventional manner to give 11 g of crude trans-1-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]-4-[2-[(2-isopropylaminoethyl)amino]ethyl]piperazine, which was used without further
15 purification in the final step:

Thiophosgene (2.8 g = 1.9 ml) was added dropwise at 5°C to a mixture of the crude product mentioned above (11 g) and triethylamine (2.8 g) in trichloroethane. The resulting mixture was stirred at room temperature for 15 min. and was then refluxed
20 for 2 hours. After evaporation in vacuo the product was purified by extraction with 1N methanesulfonic acid followed by liberation of the base with 9N sodium hydroxide as described in Example 8. The resulting oil was purified by column chromatography using silica gel and acetone-toluene -isopropylamine - ammonium hydroxide (60:40:2:2) as a mobile phase. There was obtained 1.1 g of a base,
25 which was transformed to the dimaleate salt. This salt was recrystallized twice from acetone/ether to give 0.4 g of **36**, dimaleate, mp: 156-159°C.

CHN calculated: 57.32%; 5.78%; 7.64%.

CHN found: 57.33%; 5.76%; 7.17%.

30 EXAMPLE 10

Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-3-(2-hydroxyethyl)-2-imidazolidinone, dimaleate, (Compd. **37**)

- Compound 4 (4.4 g as the base) was added to a suspension of potassium tert-butoxide (1.7 g) in dry toluene (200 ml). The mixture was kept at room temperature for 1 hour with stirring, whereupon ethylbromoacetate (2.5 g) was added. The mixture was stirred for 1 hour at room temperature and was then poured into ice.
- 5 The organic phase was separated, washed with water, dried and evaporated in vacuo. The resulting oil was dissolved in dry tetrahydrofurane (150 ml) whereupon lithium borohydride (1 g) was added. The mixture was stirred for 1 hour at room temperature and was then evaporated in vacuo. The residue was treated with ether and 1N methanesulfonic acid. The acid phase was basified with 9N sodium
- 10 hydroxide and extracted with methylene chloride. After drying and evaporation in vacuo there was obtained 2.5 g of **37**, which was converted to the maleate salt (in acetone). The salt was recrystallized from ethanol-methanol to give 1.4 pure **37**, mp: 168-170°C.
- CHN calculated: 56.78%; 5.61%; 7.79%.
- 15 CHN found: 56.45%; 5.62%; 7.83%

EXAMPLE 11

- 20 Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]piperazin-1-yl]-ethyl]-2-pyrrolidinthione, dimaleate. (Compd. 38)

- A mixture of Compound 15 (15 g) and Lawesson's reagent (5 g) in hexamethylphosphonic triamide (HMPA, 50 ml) was heated at 100°C in a N₂-atmosphere for
- 25 1.5 hours. The reaction mixture was poured into water, treated with 9N sodium hydroxide (25 ml) and extracted with ether. The etherphase was extracted with 1N methane sulphonic acid, whereupon the base was liberated with 9N sodium hydroxide and again extracted with ether. The organic phase was evaporated to give 3.5 g of an oil, which was transformed to the dimaleate salt. This salt was
- 30 recrystallized from ethanol (200 ml) to give **38**, mp: 192-193°C.
- CHN calculated: 57.42%; 5.41%; 6.09%.
- CHN found: 57.50%; 5.49%; 6.17%.

PHARMACOLOGICAL TESTS

The compounds of the invention were tested in well recognized and reliable methods. The tests were as follows, and the results are given in the following Table

5 I. The well-known 5-HT₂ antagonists, ritanserin tefludazine and irindalone, and the corresponding analogues of Compounds 1, 9 and 4, respectively, substituted in the 6-position of the indane ring system in stead of the 5-position, i.e. compounds Nos. 39, 40 and 41, were included in the tests for comparison purposes. The results of the tests are shown in the Table 1.

10

INHIBITION OF ³H-KETANSERIN BINDING TO 5-HT₂ RECEPTORS IN RAT CORTEX *IN VITRO*

By this method the inhibition by drugs of the binding of ³H-Ketanserin (0,5 nM) to Serotonin S₂ (5-HT₂) receptors in membranes from rat is determined *in vitro*.

15 Method in Hyttel, *Pharmacology & Toxicology*, **61**, 126-129, 1987.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed and cortical tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-

20 cold 50 mM tris buffer pH 7.7 (at 25°C). The centrifuge glassware used in this step has been rinsed by sonication for 10 min. in ethanol. The homogenate is centrifuged twice at 20,000 g for 10 min. at 4°C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 500 vol (w/v) ice-cold buffer.

25 Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 2000 µl of tissue suspension (final tissue content corresponds to 4 mg original tissue). The binding experiment is initiated by addition of 100 µl of ³H-Ketanserin (final concentration 0.5 nM) and by placing the tubes in a 37°C water bath. After incubation for 30 min. the samples are filtered under vacuum

30 (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid

scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 μ M mianserin.

For determination of the inhibition of binding five concentrations of drugs covering 3
5 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC_{50} value is determined as the concentration at which the binding is 50% of the total binding in control samples
10 minus the nonspecific binding in the presence of 1 μ M mianserin.

3H -Ketanserin = [ethylene- 3H]-ketanserin hydrochloride from New England Nuclear, specific activity 60-80 Ci/mmol).

15 INHIBITION OF 3H -SPIPERONE BINDING TO DOPAMINE D-2 RECEPTORS IN RAT CORPUS STRIATUM *IN VITRO*

By this method the inhibition by drugs of the binding of 3H -spiperone (0.5 nM) to dopamine D-2 receptors in membranes from rat corpus striatum is determined *in vitro*. Method and results in Hyttel & Larsen, *J. Neurochem*, **44**, 1615-1622, 1985).

20

Procedure

Male Wistar (Mol:Wistar) rats (125-250 g) are sacrificed and striatal tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 mM K-phosphate buffer pH 7.4 (at 25°C). The homogenate is
25 centrifuged twice at 20,000 g for 10 min. at 4°C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 1300 μ l (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 μ l of drug solution in water (or
30 water for total binding) and 4000 μ l of tissue suspension (final tissue content corresponds to 3.08 mg original tissue). The binding experimental is initiated by addition of 100 μ l of 3H -spiperone (final concentration 0.5 nM) and by placing the tubes in a 37°C water bath. After incubation for 10 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are

rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 10 μ M of 6,7-ADTN.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

10

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC₅₀ value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 10 μ M of 6,7-ADTN.

15

³H-Spiperone = [phenyl-4-³H]-spiperone from Amersham International plc. England, specific activity 15-25 Ci/mmol.

INHIBITION OF ³H-PRAZOSIN BINDING TO α_1 ADRENOCEPTORS IN RAT

20 BRAIN *IN VITRO*

By this method the inhibition of the binding of ³H-Prazosin (0.25 nM) to α_1 adrenoceptors in membranes from rat brain is determined *in vitro*. Method and results in Hyttel & Larsen, *J. Neurochem*, **44**, 1615-1622, 1985; Skarsfeldt & Hyttel, *Eur. J. Pharmacol.* **125**, 323-340, 1986.

25

Procedure

Male Wistar (Mol:Wist) rats (125-200 g) are sacrificed and brain tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 nM Tris buffer pH 7.7 (at 25°C). The homogenate is centrifuged twice at 20,000 g for 10 min. at 4°C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 400 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 μ l of drug solution in water (or water for total binding) and 4000 μ l of tissue suspension (final tissue content corresponds to 10 mg original tissue). The binding experiment is initiated by addition of 100 μ l of 3 H-Prazosin (final concentration 0.25 nM) and by placing the tubes in a
5 25°C water bath. After incubation for 20 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which then are poured on the filters. Thereafter, the filters are washed with 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. PicofluorTM15) are added. After shaking for 1 h
10 and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 μ M of Prazosin.

For determination of the inhibition of binding five concentrations of drugs covering 3
15 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC₅₀ value is determined as the concentration at which the binding is 50% of the total binding in control samples
20 minus the nonspecific binding in the presence of 1 μ M of Prazosin.

3 H-Prazosin = [furoyl-5- 3 H]-Prazosin from New England Nuclear, specific activity approximately 20 Ci/mmol.

TABLE 1
Receptor Binding ; IC₅₀(nM)

| Compound No. | 5-HT ₂ 3H-Ket | DA D-2 3H-Spi | α ₁ 3H-Praz |
|--------------|-----------------------------|------------------|---------------------------|
| 1 | 2.9 | 760 | 320 |
| (+)-1 | 2.0 | 290 | 330 |
| 2 | 21 | 1100 | 150 |
| (+)-2 | 12 | 330 | 72 |
| (-)-2 | 500 | 22000 | 1100 |
| 3 | 25 | 2200 | 230 |
| (-)-3 | 11 | 370 | 210 |
| (+)-3 | 230 | 6300 | 2500 |
| 4 | 2.9 | 360 | 200 |
| 5 | 8.9 | 1300 | 380 |
| 6 | 56 | 2600 | 1000 |
| 7 | 7.9 | 2800 | 240 |
| 8 | 12 | 1000 | 270 |
| 9 | 3.7 | 370 | 220 |
| 10 | 11 | 2500 | 840 |
| (-)-10 | 15 | 730 | 390 |
| (+)-10 | 3300 | 28000 | |
| 11 | 3.9 | 280 | 260 |
| (+)-11 | 75 | 1300 | 340 |
| (-)-11 | 1.1 | 200 | 210 |
| 12 | 3.0 | 450 | 120 |
| 13 | 3.7 | 510 | 350 |
| 14 | 23 | 550 | 140 |
| 15 | 10 | 500 | 370 |
| 16 | 10 | 160 | 73 |
| 17 | 44 | 300 | 310 |
| 18 | 2.8 | 190 | 600 |
| 19 | 2.6 | 260 | 240 |

TABLE 1 (cont'd)
Receptor Binding ; IC₅₀(nM)

| Compound No. | 5-HT ₂ 3H-Ket | DA D-2 3H-Spi | α ₁ 3H-Praz |
|--------------|-----------------------------|------------------|---------------------------|
| 20 | 9.9 | 750 | 510 |
| 21 | 3.5 | 920 | 670 |
| 22 | 3.5 | 1100 | 240 |
| 23 | 4.0 | 720 | 250 |
| 24 | 6.4 | 240 | 270 |
| 25 | 5.6 | 110 | 66 |
| 26 | 11 | 450 | 60 |
| 27 | 15 | 280 | 180 |
| 28 | 26 | 490 | 970 |
| 29 | 1.5 | 230 | 110 |
| 30 | 1.7 | 220 | 110 |
| (+)-30 | 0.95 | 140 | 43 |
| (-)-30 | 42 | 2900 | |
| 31 | 1.5 | 67 | 52 |
| 32 | 1.5 | 93 | 170 |
| (+)-32 | 21 | 490 | 350 |
| (-)-32 | 0.75 | 33 | 67 |
| (+)-33 | 1.1 | 280 | 41 |
| (-)-33 | 57 | 4600 | |
| (+)-34 | 120 | 1700 | |
| (-)-34 | 1.3 | 94 | 62 |
| 35 | 4.8 | 150 | 120 |
| 36 | 3.6 | 260 | 69 |
| 37 | 6.1 | 320 | 710 |
| 38 | 5.3 | 290 | 260 |

TABLE 1 (cont'd)
Receptor Binding ; IC₅₀(nM)

| Compound No. | 5-HT ₂ 3H-Ket | DA D-2 3H-Spi | α ₁ 3H-Praz |
|--------------|-----------------------------|------------------|---------------------------|
| Tefludazine | 4.6 | 10 | 17 |
| Irindalon | 3.4 | 400 | 16 |
| Ritanserin | 0.40 | 12 | 47 |
| 39 | | 21 | 8.3 |
| 40 | 0.71 | 43 | 12 |
| 41 | | 17 | 3.1 |

QUIPAZINE INHIBITION

Quipazine is a 5-HT₂ agonist, which induces head twitches in rats. The test is an *in vivo* test for 5-HT₂-antagonistic effect testing the ability to inhibit head twitches. The method and test results for some reference substances are published by Arnt et al. (*Drug Development Research*, **16**, 59-70, 1989).

In this test the compounds showed effects with ED₅₀ values down to 0.01 mg/kg..

10 LIGHT/DARK DISCRIMINATION TEST IN MICE

This test was carried out in accordance with the method described in Costall et al. *Br. J. Pharmacol.* **90** 275P (1987).

- 15 The test was conducted using a two compartment activity box in which the actions of anxiolytic compounds to reduce aversion against a brightly-lit environment may be readily detected. The box is designed as an open-top experimental box (45*27*27cm) one third of which was partitioned from the rest, painted black and illuminated with red light. The remainder of the box was painted white and brightly
- 20 illuminated (1000 W). The floor of each area was lined into squares. Behavioural changes were determined for each area from video recordings for periods of 40 min.

Data obtained from dose groups of 5 animals (male albino BKW mice, 25 - 30 g) were analysed using single factor analysis of variance, and Dunnett's t-test. Test compounds were given intraperitoneally 45 min before testing. In this test model Compounds (+)-30, (-)-32 and (+)-33 showed significant anxiolytic activity ($p < 0.05$) in doses from 0.01 to 1 mg/kg.

LIGHT/DARK DISCRIMINATION TEST IN RATS.

The test was carried out similarly to the test in mice described above, however modified in accordance with F.C.Colpaert et al., Psychopharmacology (1985) 86: 45-54. The test used Wistar WU rats. In this test model Compounds (-)-32 and (+)-33 showed significant anxiolytic activity ($p < 0.05$) in doses from 0.1 to 1 mg/kg.

All the compounds except the weak or inactive stereoisomers of Compd. 2, 3, 10, 11, 30, 32, 33, and 34 show high affinity to 5-HT₂ receptors and have much lower affinity to D-2 receptors and α_1 adrenoceptors than the prior art compounds included in the tests for comparison purposes. Tefludazine, a 6-substituted 1-piperazino-3-phenylindan derivative representative for US Patent 4,443,448, shows high affinity to all three receptor types whereas irindalone, a 1-piperazino-3-(fluorophenyl)indan derivative representative for US patent 4,684,650, in addition to a high affinity to 5-HT₂ receptors has a significant affinity to α_1 adrenoceptors. The dramatic effect of the change from 6- to 5-substitution is illustrated by comparison of the receptor profiles of the 6-substituted derivatives 39, 40 and 41 with their otherwise identical 5-substituted analogues 1, 9 and 4.

25

FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes

such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

10

1) Tablets containing 5 milligrams of Compound 4c calculated as the free base:

| | | |
|----|--------------------|--------|
| | Comp. (+)-33 | 5 mg |
| | Lactose | 18 mg |
| 15 | Potato starch | 27 mg |
| | Sucrose | 58 mg |
| | Sorbitol | 3 mg |
| | Talcum | 5 mg |
| | Gelatine | 2 mg |
| 20 | Povidone | 1 mg |
| | Magnesium stearate | 0.5 mg |

2) Tablets containing 50 milligrams of Compound 4b calculated as the free base:

| | | |
|----|--------------------|--------|
| 25 | Comp. (+)-30 | 50 mg |
| | Lactose | 16 mg |
| | Potato starch | 45 mg |
| | Sucrose | 106 mg |
| | Sorbitol | 6 mg |
| 30 | Talcum | 9 mg |
| | Gelatine | 4 mg |
| | Povidone | 3 mg |
| | Magnesium stearate | 0.6 mg |

3) Syrup containing per milliliter:

| | | |
|----|----------------|----------|
| | Comp. (–)-32 | 10 mg |
| | Sorbitol | 500 mg |
| 5 | Tragacanth | 7 mg |
| | Glycerol | 50 mg |
| | Methyl-paraben | 1 mg |
| | Propyl-paraben | 0.1 mg |
| | Ethanol | 0.005 ml |
| 10 | Water | ad 1 ml |

4) Solution for injection containing per milliliter:

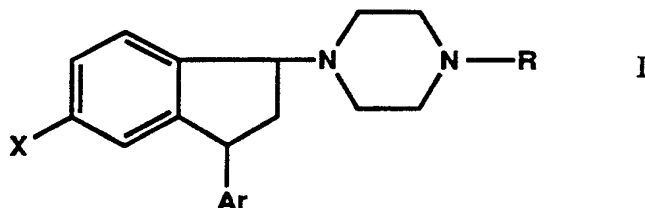
| | | |
|----|---------------|---------|
| | Comp. (–)-34 | 50 mg |
| 15 | Acetic acid | 17.9 mg |
| | Sterile water | ad 1 ml |

5) Solution for injection containing per milliliter:

| | | |
|----|------------------|---------|
| 20 | Comp. (–)-11 | 10 mg |
| | Sorbitol | 42.9 mg |
| | Acetic acid | 0.63 mg |
| | Sodium hydroxide | 22 mg |
| | Sterile water | ad 1 ml |
| 25 | | |

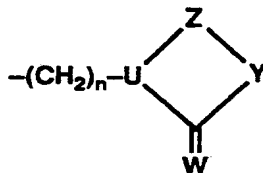
PATENT CLAIMS

1. A 5-Substituted trans-1-piperazinoindan derivative having the general formula :



5 wherein X is halogen, trifluoromethyl, lower alkyl, lower alkylthio, lower alkyloxy, hydroxy, lower alkylsulphonyl, lower alkyl- or dialkylamino, trifluoromethylthio or a cyano group;

R is hydrogen, lower alkyl or alkenyl, cycloalkyl, or cycloalkyl lower alkyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R is a substituent



wherein n is an integer from 1 to 6;

15 U is CH or N;

Y is CH₂, O, S or N-R¹, R¹ being hydrogen or a cycloalkyl or a cycloalkylmethyl or a lower alkyl or alkenyl group optionally substituted with one or two hydroxy groups or a phenyl group optionally substituted with halogen, trifluoromethyl or lower alkyl;

W is O or S;

20 Z is -(CH₂)₄-, $\text{--CH}_2\text{--}\overset{\text{R}^2}{\underset{\text{R}^3}{\text{C}}}\text{--}$, $\text{--CH}_2\text{--}\overset{\text{R}^2}{\underset{\text{R}^3}{\text{C}}}\text{--CH}_2\text{--}$, wherein R² and R³ are hydrogen or lower

alkyl, -CH=CH-CH₂-, -CH=CH-, 1,2-phenylene, optionally substituted with halogen or trifluoromethyl, or if U is nitrogen and Y is NR¹ Z may also be 1,2-C₆H₄CH₂- (to form a quinazolidinone or -thione ring system) or 1,2-C₆H₄CO- (to form a quinazolidinone or thioxoquinazolidinone ring system) and

Ar is a phenyl ring optionally substituted with halogen, trifluoromethyl or lower alkyl or Ar is a thiophene or furane ring optionally substituted with lower alkyl;

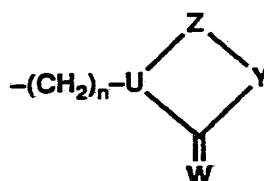
with the proviso that when Ar is optionally substituted phenyl, R may not be hydro-
5 gen or lower alkyl or alkenyl optionally substituted with hydroxy;

or a pharmaceutically acceptable acid addition salt or prodrug thereof.

2. A 5-Substituted trans-1-piperazinoindan derivative according to Claim 1, **charac-**
10 **terized in** that Ar is a phenyl group optionally substituted with halogen or methyl, preferably 4-fluorophenyl, and/or that X is Cl or F.

3. A 5-Substituted trans-1-piperazinoindan derivative according to Claim 1 or 2, **characterized in** that R is a group of the formula:

15



wherein n is 2, U is N; W is O or S; Z is -CH₂-CH₂- or -CH₂-CH₂-CH₂-; and Y is a group NR¹ wherein R¹ is hydrogen or lower alkyl.

4. A 5-Substituted trans-1-piperazinoindan derivative according to Claim 1,
20 **characterized in** that it is selected from the group of:

(-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]-ethyl]-3-isopropyl-2-imidazolidinone, dimaleate;

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione, dihydrochloride;

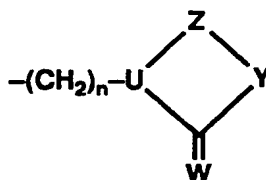
25 (-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinethione, dihydrochloride;

(+)-Trans-1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone, dimaleate; and

30 (-)-Trans-1-[2-[4-[5-chloro-3-(4-fluorophenyl)-2,3-dihydro-1*H*-inden-1-yl]piperazin-1-yl]ethyl]-tetrahydro-2(1*H*)-pyrimidinone, dimaleate;

and acid addition salts thereof.

5. A prodrug for a compound of Claim 1 in which R is a group of the formula:



- wherein W is O and Y is NR¹, R¹ being hydrogen, and n, Z and U are as defined in Claim 1, **characterized in** that it is a reaction product with an acid or an activated acid, with formaldehyde alone or in the presence of an alcohol or an amine, or with an acyloxymethylene halide, which product accordingly may be represented by a formula similar to the general Formula I defined in Claim 1 wherein W is O, Y however being a group NR^{1'} wherein R^{1'} designates a group **-A-B** where A is selected from CO, CS, or CH₂, and
- 10 if A is CO or CS, B is selected from the groups consisting of:
- i) hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl or cycloalk(en)ylalk(en)yl, optionally substituted with one or two hydroxy groups, or phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, acyloxy, or cyano; or
 - 15 ii) QB¹, wherein Q is O or S and B¹ is selected from the substituents defined for B under i) above except hydrogen; and
 - iii) NB²B³, wherein B² and B³ independently are selected from the substituents defined for B¹ under ii) above, or B² and B³ are combined to form a four to eight
 - 20 membered heterocyclic ring containing from one to three nitrogen atoms and from zero to three oxygen or sulfur atoms; or
- if A is CH₂, B is selected from the groups consisting of:
- iv) a group QB¹ as defined in ii);
 - v) a group NB²B³ as defined in iii); or
 - 25 vi) a group OC(O)B⁴, wherein B⁴ is as defined for B¹;

6. Pharmaceutical preparation, **characterized in** that it comprises at least one compound according to Claims 1 together with a pharmaceutically acceptable carrier or diluent.

7. Pharmaceutical preparation according to Claim 6, **characterized in** that it comprises a prodrug according to Claim 5 in a pharmaceutically acceptable oil.

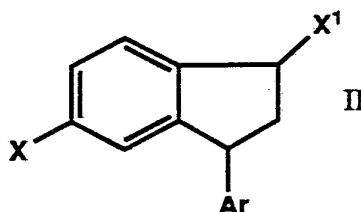
8. Use of a 5-Substituted trans-1-piperazinoindan derivative having the general Formula I as defined in Claim 1, except that the proviso in Claim 1 does not apply, or a pharmaceutically acceptable acid addition salt thereof or a prodrug therefor for the manufacture of a medicament for the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia or migraine.

10 9. Method for the treatment of anxiety, depression, sleeping disorders, negative symptoms of schizophrenia or migraine, comprising administration of a compound of the Formula I as defined in Claim 1, except that the proviso in Claim 1 does not apply, or a pharmaceutically acceptable acid addition salt thereof or a prodrug therefor to a patient in need thereof in a therapeutically effective amount.

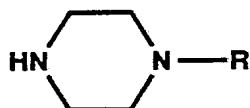
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10. Method for the preparation of a 5-Substituted trans-1-piperazinoindan derivative according to Claim 1 **characterised in** that it comprises:

a) treating a compound of the following Formula II:



20 with a piperazine derivative of formula:

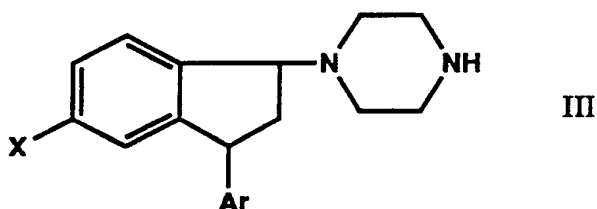


in which formulas X, Ar and R are as defined above, and X¹ is halogen or -OSO₂R⁴ wherein R⁴ is alkyl such as CH₃ or aryl such as p-toluyI;

25

b) treating a compound of the following Formula III:

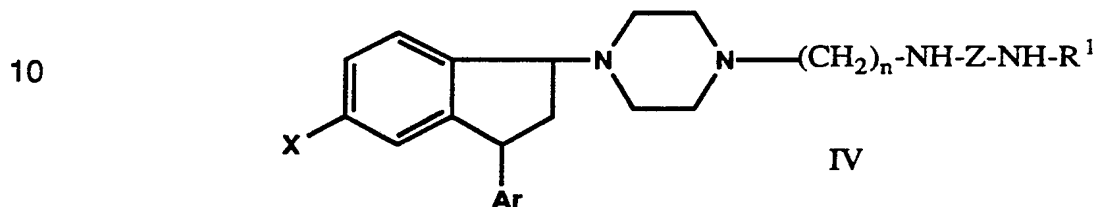
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wherein X and Ar are as defined above, with a compound of the formula X^1-R wherein R and X^1 are as defined above except that R cannot be hydrogen;

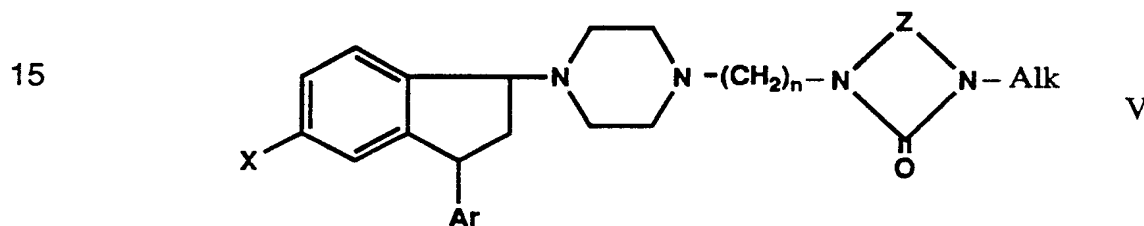
- 5 c) treating a compound of Formula III with a compound $R'-CHO$, wherein R' is such a group that $R'-CH_2-$ is as defined above for R, in the presence of a reducing agent eg. $NaCNBH_3$ or hydrogen in the presence of a suitable catalyst such as Pt or Pd;

- d) treating a compound of the following Formula IV:



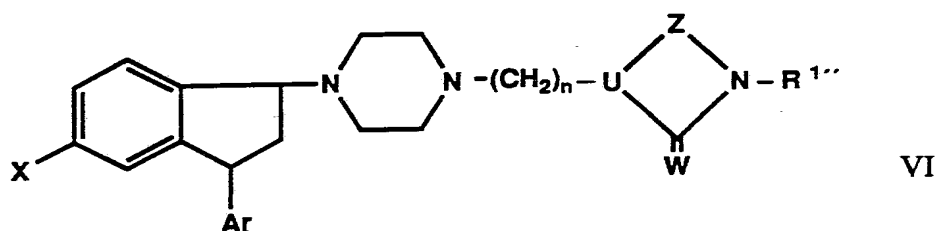
wherein X, Ar, R^1 , Z and n are as defined above, with CS_2 , thiophosgene, urea or phosgene;

- e) treating a compound of the following Formula V:



wherein X, Ar, n, and Z are as defined above and Alk is an alkali metal such as sodium or potassium, with a compound of formula R^5-X^1 wherein R^5 is a lower alkyl group and X^1 is as defined above;

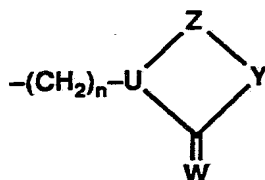
- 20 f) reducing a compound with the following Formula VI:



wherein X, Ar, n, U, Z and W are as defined above and R^{1''} is a cycloalkyl or lower alkyl group containing one or more ester, ketone or aldehyde groups with a suitable reducing agent to a corresponding compound wherein R¹ is a lower alkyl or a

5 cycloalkyl group containing one or more hydroxy groups;

g) reacting a compound of Formula I wherein R is a group of the formula:



10 wherein n, U, Z and Y are as defined above and W is O, with P₂S₅ or Lawesson's reagent to obtain the corresponding compound wherein W is S;

and if desired subsequently transferring the derivative obtained in a corresponding acid addition salt.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 91/00358

| | | |
|--|---|-------------------------------------|
| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ | | |
| According to International Patent Classification (IPC) or to both National Classification and IPC | | |
| IPC5: A 61 K 31/495, C 07 D 207/24, 207/27, 233/30, 233/36, 239/22 263/20, 295/073, 295/088, 333/20 | | |
| II. FIELDS SEARCHED | | |
| Minimum Documentation Searched ⁷ | | |
| Classification System | Classification Symbols | |
| IPC5 | C 07 D | |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸ | | |
| SE,DK,FI,NO classes as above | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ | | |
| Category * | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ |
| A | US, A, 4684650 (KLAUS P. BØGESØ) 4 August 1987, see the whole document -- | 1-8, 10 |
| A | US, A, 4443448 (KLAUS P. BØGESØ) 17 April 1984, see the whole document -- | 1-8, 10 |
| A | J. Med. Chem., Vol. 31, 1988 Klaus P. Bøgesø et al: "Antihypertensive Activity in a Series of 1-Piperazino-3-phenylindans with Potent 5-HT2-Antagonistic Activity", see page 2247 - page 2256 -- ----- | 1-8, 10 |
| <p>* Special categories of cited documents:¹⁰</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> | | |
| IV. CERTIFICATION | | |
| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | |
| 17th March 1992 | 1992 -03- 18 | |
| International Searching Authority | Signature of Authorized Officer | |
| SWEDISH PATENT OFFICE | Irja Berlin | |

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim number 9, because ^{it s/} ~~they relate to~~ subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☒ Claim number 5, because ^{it s/} ~~they relate to~~ parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See next sheet.

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED

The wordings "B is selected from the groups consisting of:

i) ... acyloxy" and

"NB²B³.... or B² and B³ are combined to form a four to eight membered heterocyclic ring containing from one to three nitrogen atoms and from zero to three oxygen or sulfur atoms" in claim 5 are too broadly formulated to permit an adequate search.

The search has therefore essentially been restricted to those compounds of formula I which are supported by the examples.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 91/00358

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 28/02/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| US-A- 4684650 | 87-08-04 | AU-B- 595167 | 90-03-29 |
| | | AU-D- 4796590 | 90-05-10 |
| | | AU-D- 4910685 | 86-05-01 |
| | | CA-A- 1247098 | 88-12-20 |
| | | EP-A-B- 0183349 | 86-06-04 |
| | | JP-A- 61171466 | 86-08-02 |
| US-A- 4443448 | 84-04-17 | AU-B- 538424 | 84-08-16 |
| | | AU-D- 6791781 | 82-09-16 |
| | | CA-A- 1181750 | 85-01-29 |
| | | EP-A-B- 0035363 | 81-09-09 |
| | | GB-A-B- 2071088 | 81-09-16 |
| | | JP-C- 1600624 | 91-01-31 |
| | | JP-B- 2024819 | 90-05-30 |
| | | JP-A- 56167670 | 81-12-23 |